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ORIGINAL REPORT

Phase II Trial of Bevacizumab in Recurrent or Persistent Endometrial Cancer: A Gynecologic Oncology Group Study

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ABSTRACT

Purpose
Bevacizumab, a recombinant humanized monoclonal antibody against vascular endothelial growth factor-A (VEGF-A), has clinical activity in multiple tumor types. We conducted a phase II trial to assess the activity and tolerability of single-agent bevacizumab in recurrent or persistent endometrial cancer (EMC).

Patients and Methods
Eligible patients had persistent or recurrent EMC after receiving one to two prior cytotoxic regimens, measurable disease, and Gynecologic Oncology Group performance status of ≤ 2. Treatment consisted of bevacizumab 15 mg/kg intravenously every 3 weeks until disease progression or prohibitive toxicity. VEGF-A was assessed by immunohistochemistry in archival tumor and by enzyme-linked immunosorbent assay in pretreatment plasma. Primary end points were progression-free survival (PFS) at 6 months and overall response rate.

Results
Fifty-six patients were enrolled. Fifty-two patients were eligible and evaluable. Median age was 62 years, and prior treatment consisted of one or two regimens in 33 (63.5%) and 19 (36.5%) patients, respectively. Twenty-nine patients (55.8%) received prior radiation. Adverse events were consistent with those expected with bevacizumab treatment. No GI perforations or fistulae were seen. Seven patients (13.5%) experienced clinical responses (one complete response and six partial responses; median response duration, 6.0 months), and 21 patients (40.4%) survived progression free for at least 6 months. Median PFS and overall survival times were 4.2 and 10.5 months, respectively. Suggested associations were observed between high VEGF-A and adjusted hazard of death or tumor response when evaluated in tumor/plasma or plasma, respectively.

Conclusion
Bevacizumab is well tolerated and active based on PFS at 6 months in recurrent or persistent EMC and warrants further investigation.

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INTRODUCTION

Endometrial cancer affects an estimated 40,000 women in the United States every year, and long-term outcomes for patients with advanced-stage or recurrent disease are poor.[1] Investigations focusing on new approaches to improve outcomes in this patient population are warranted.

There have been several randomized studies addressing the issue of optimal therapy for this group of patients. The most recently reported study randomly assigned 263 patients to doxorubicin and cisplatin (AP) versus paclitaxel, doxorubicin, and cisplatin (TAP). TAP was superior to AP in terms of overall response rate (ORR; 57% *v* 34%, respectively; $P < .01$), median progression-free survival (PFS; 8.3 *v* 5.3 months, respectively; $P < .01$), and median overall survival (15.3 *v* 12.3 months, respectively; $P = .037$).[2] This improved efficacy came at the cost of increased toxicity. In an attempt to address this issue, a study of TAP compared with paclitaxel and carboplatin has completed accrual and is in follow-up (ClinicalTrials.gov identifier: NCT00063999). Once this initial therapy has been delivered, there are limited treatment options. Hormonal therapies, when given to chemotherapy-naive patients, can result in responses, but these responses are of short duration.[3-7] Targeted therapies, other than hormonal therapies, have yet to be implemented in clinical practice. Completed studies have evaluated agents that target mammalian target of rapamycin (temsirolimus,[8,9] everolimus,[10] and ridaforolimus[11]), human epidermal growth factor receptor 2 (trastuzumab[12]), epidermal growth factor

receptor (erlotinib,[13] gefitinib,[14] and cetuximab[15]), and vascular endothelial growth factor (VEGF; sunitinib,[16] sorafenib,[17] and thalidomide[18]), showing none to modest activity.

Bevacizumab monotherapy has been evaluated in persistent or recurrent ovarian and cervical cancers with positive results. A phase II trial of bevacizumab in patients with ovarian cancer (one to two prior chemotherapy regimens) demonstrated a single-agent response rate of 21%, with 40.3% of patients surviving progression free for at least 6 months.[19] A second phase II trial in patients with platinum-resistant ovarian cancer (one to three prior chemotherapy regimens) demonstrated a response rate of 15.9%.[20] In patients with cervical cancer (one or two prior chemotherapy regimens), a response rate of 10.9% was observed, with 23.9% of patients surviving progression free for at least 6 months.[21]

A phase II trial of single-agent bevacizumab was conducted in patients with recurrent or persistent EMC. The primary objective was to evaluate efficacy in terms of both the probability of surviving progression free for at least 6 months (PFS at 6 months) and clinical response.

PATIENTS AND METHODS

Patient Selection

Eligible patients met the following criteria: histologic confirmation of the primary tumor by central pathology review by the Gynecologic Oncology Group (GOG) Pathology Committee; GOG performance status of 0 to 2; measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST)[22]; one or two prior cytotoxic regimens; discontinuation of prior chemotherapy at least 3 weeks before registration and hormonal therapy at least 1 week before registration; recovery of the effects of recent surgery, radiotherapy, or chemotherapy; freedom from active infection requiring antibiotics; adequate hematologic (absolute neutrophil count $\geq$ 1,000/μL and platelets $\geq$ 100,000/μL), renal (serum creatinine $\leq$ 1.5$\times$ the institutional upper limit of normal [ULN] and urine protein-to-creatinine ratio $<$ 1), hepatic (serum bilirubin $\leq$ 1.5$\times$ ULN and AST and alkaline phosphatase $\leq$ 2.5$\times$ ULN), and coagulation (prothrombin time such that international normalized ratio $\leq$ 1.5 or between 2 and 3 for patients receiving stable doses of therapeutic warfarin, and partial thromboplastin time $\leq$ 1.5$\times$ ULN) laboratory values; left ventricular ejection fraction $\geq$ 50% (for patients who received prior anthracycline); negative serum pregnancy test before study entry and agreement to practice an effective form of contraception in patients of childbearing potential; a signed approved informed consent in accordance with federal, state, and local requirements; and authorization permitting release of personal health information.

Patients were ineligible if they met any of the following criteria: prior treatment with bevacizumab or other VEGF pathway–targeted therapy; prior treatment with any noncytotoxic therapy (other than hormonal therapy); other malignancies (except nonmelanomatous skin cancer) evident within 5 years or prior cancer treatment that contradicts eligibility; nonhealing wound, ulcer, or bone fracture; abdominal fistula, GI perforation, or intra-abdominal abscess within 28 days; active bleeding or pathologic condition that carries high risk of bleeding; known CNS disease; clinically significant cardiovascular disease; and major surgical procedure within 28 days or anticipated on study.

Treatment

Enrolled patients were to receive bevacizumab 15 mg/kg intravenously every 21 days with no dose modification except for at least a 10% change in body weight. Treatment was planned until disease progression or adverse events prohibited further therapy. Toxicity was monitored with history, physical examination, and laboratory assessment before each treatment cycle, with adverse events defined and graded according to Common Terminology Criteria for Adverse Events (version 3.0). Bevacizumab was held for grade 3 nonhematologic toxicity for a maximum of 4 weeks to allow recovery to $\leq$ grade 1. Bevacizumab was discontinued for grade 4 allergic reactions; grade 2 (new or worsened) and 3 to 4 arterial thrombosis; symptomatic grade 4 venous thrombosis; grade 4 hypertension; grade 4 (or nephrotic syndrome) proteinuria; grade 4 hemorrhage; GI perforation, GI leak, or fistula; and reversible posterior leukoencephalopathy syndrome. Specific guidelines were implemented for modifying the treatment regimen in the event of hypertension, venous thrombosis, proteinuria, and hemorrhage.

Evaluation Criteria

Activity of bevacizumab was assessed according to RECIST[16] either by palpation before each cycle or by computed tomography or magnetic resonance imaging at baseline, every other cycle for the first 6 months, and every four cycles thereafter.

VEGF-A Assessments

VEGF-A expression was detected by immunohistochemistry in archival formalin-fixed, paraffin-embedded primary, metastatic, or recurrent tumor using antigen retrieval (30 minutes in 1 mmol/L EDTA in a Nordicware pressure cooker) and the Ventana NexES automated immunohistochemistry staining system with the SC-152 (A-20) primary antibody against VEGF-A (Santa Cruz Biotechnology, Santa Cruz, CA). Controls for the immunohistochemistry assay included formalin-fixed, paraffin-embedded MCF7-WT human breast cancer cells and poorly differentiated endometrial cancer cells for high VEGF-A; doxorubicin-resistant MCF7-40F human breast cancer cells and well-differentiated endometrial cancer cells for low VEGF-A; and invasive breast carcinomas that do not express VEGF-A. Cytoplasmic VEGF-A staining was categorized by intensity (0 to 3+ relative to the negative controls and controls for high VEGF-A) and percent positive tumor cells (0% to 100%). VEGF-A concentration was quantified in picograms per milliliter by enzyme-linked immunosorbent assay (ELISA) using the DVE00 quantikine human VEGF immunoassay (R&D Systems, Minneapolis, MN) and recombinant human VEGF as instructed and previously described[9] in pretreatment plasma prepared from blood drawn in a purple-top tube with EDTA. Assays for VEGF-A were performed by the GOG Core Laboratory for Targets and Receptors under the direction and supervision of the director (K.K.L.).

Statistics

The primary objective evaluated the efficacy of bevacizumab through the frequency of patients with objective tumor responses and the frequency of patients who survived progression free for at least 6 months. The null hypothesis relating to uninteresting levels of activity was determined from an analysis of a historical data set based on a similar population of patients where the levels of activity were believed to be inactive to modestly active (Table 1). The null hypothesis jointly specified the probability of a patient experiencing a tumor response to within $\leq$ 10% and the probability of a patient being progression free at 6 months to within $\leq$ 15%. Clinically significant differences were 20% increases in the probability of either event (ie, probability of 30% or 35%, respectively). Using a method by Sill and Yothers,[32] a two-stage design was used with a goal of limiting patient exposure to inactive agents while restricting the probabilities of type I and type II errors to approximately 10%. Nineteen patients were targeted for accrual to the first stage, but the number was allowed to deviate for administrative flexibility. If the regimen demonstrated sufficient activity ($>$ two or three patients with responses or PFS at 6 months, respectively), then the study targeted 42 patients (cumulatively) in stage 2. If more than seven or 10 patients had responses or were alive and progression free at 6 months, respectively, the regimen was deemed worthy of further study.

Biomarkers were screened for associations with demographic characteristics and clinical outcomes in an exploratory fashion to yield hypotheses for further testing. Characteristics of interest included age, performance status, prior treatment, cell grade, response, PFS at 6 months, and the hazards of progression and death. Where appropriate, biomarkers were dichotomized into high versus low values using the observed median as a threshold. Some characteristics were examined as ordinal categorical variables (eg, response with progressive disease $<$ stable disease $<$ response). Associations were

Table 1. Historical Control Characteristics

Protocol	Agent	No. of Evaluable Patients	Probability PFS at 6 Months		Response	
			Product Limit Estimate	SE	No. of Patients	%
GOG 129-B[23]	Etoposide	25	0.08	0.05	0	0
GOG 129-C[24]	Paclitaxel	48	0.21	0.06	12	25
GOG 129-E[25]	Dactinomycin	27	0.04	0.04	3	11
GOG 129-H[26]	Liposomal doxorubicin	43	0.23	0.06	4	9
GOG 129-I[27]	Pyrazoloacridine	25	0.16	0.07	1	4
GOG 129-J[28]	Topotecan	28	0.25	0.08	2	7
GOG 129-K[29]	Oxaliplatin	52	0.27	0.06	7	13
GOG 129-L[30]	Irofulven	25	0.28	0.09	1	4
GOG 129-M[31]	Flavopiridol	21	0	0	0	0
GOG 229-B[18]	Thalidomide	24	0.08	0.06	3	12
GOG 229-E	Bevacizumab	52	0.40	0.07	7	13.5

Abbreviations: PFS, progression-free survival; GOG, Gynecologic Oncology Group.

examined with correlations (Kendall's τ-b and Spearman rank correlation coefficient), χ^2 tests, and the Cox proportional hazards model. If $P < .05$, an association was designated as suggested. Given the small sample sizes, a lack of a suggested association should not be interpreted as definitive.

RESULTS

Patient Characteristics

From March 2006 to October 2007, GOG member institutions enrolled 56 patients onto this trial. Four patients were deemed ineligible because of second primary cancers (n = 2), inadequate pathology for central review (n = 1), and wrong primary cancer (n = 1); the remaining 52 patients were assessable for toxicity and response. Patient characteristics are listed in Table 2. A total of 368 cycles were administered, and a median of five cycles were given (range, one to 27 cycles). Twenty patients (38.5%) received eight or more cycles.

Adverse Events

As shown in Table 3, safety of bevacizumab in all 52 patients was analyzed descriptively. No GI perforations or fistulae were reported. No treatment-related deaths were reported. One patient had a grade 4 hemorrhage of the stomach, and another patient had a grade 3 hemorrhage of the rectum. Two patients had grade 3 or 4 thrombosis/embolism. One patient had an asymptomatic pulmonary embolus noted on routine computed tomography scan after cycle 2 and was then removed from study after cycle 3 for a new deep venous thrombosis that developed on warfarin. The second patient developed a deep venous thrombosis after cycle 2 and continued study treatment once anticoagulation was instituted. Two patients had grade 3 or 4 proteinuria, and four patients had grade 3 hypertension. One episode of grade 3 hypotension was reported. One patient had grade 2 left ventricular systolic function decrease (comorbidities included prior anthracycline, coronary artery disease, elevated cholesterol, hypertension, and diabetes). The treating investigator listed this adverse event as possibly related to bevacizumab and possibly related to the comorbidities. One patient had a small bowel obstruction. Three patients were removed from study as a result of toxicity (one patient each for recurrent thrombosis, hemoptysis [grade 1, lung metastases], and proteinuria).

Activity of Bevacizumab

The activity of bevacizumab was analyzed in 52 patients (Table 2). One complete response and six partial responses were observed, for an ORR of 13.5% (90% CI for the true response rate, 6.5% to 27%), with median response duration of 6 months. The histologic subtypes of the observed responses were high-grade serous carcinoma for the complete response and three high-grade serous carcinomas, one endometrioid carcinoma, one clear cell carcinoma, and one adenocarcinoma unspecified for the partial responses. Twenty-one (40.4%; 90% CI for the true proportion, 29% to 53%) of 52 patients were progression free for at least 6 months. The percentage of patients surviving progression free for at least 6 months did not vary significantly across histologic subtype (35% *v* 36% for endometrioid and high-grade serous carcinomas, respectively). Figure 1 indicates that the median PFS in the study population was 4.17 months. The median overall survival was 10.55 months.

VEGF-A

Immunohistochemical expression of VEGF-A was examined in 40 primary, two metastatic, and two recurrent tumors from 44 of 52 patients. VEGF-A staining intensity was low in 34% (four were negative, and 11 had 1+ staining) and high in 66% (17 exhibited 2+ staining, and 12 displayed 3+ staining) of tumors. The percentage of VEGF-A–positive tumor cells varied from 0% to 100% and was categorized at the median (35%). VEGF-A concentration, quantified by ELISA in pretreatment plasma from 34 of 52 patients, ranged from less than the lower limit of detection (5 pg/mL) to 856 pg/mL and was categorized at the median as low ($<$ 76.9 pg/mL) versus high ($\geq$ 76.9 pg/mL). Of the various associations examined in Appendix Tables A1 and A2 (online only) and Figure 2, a suggested association was observed between high VEGF-A staining intensity (categorized at the median as high or low) and a reduced risk of death (adjusted hazard ratio [HR], 0.350; 95% CI, 0.153 to 0.797), high pretreatment plasma VEGF-A and lack of tumor response ($r = -0.382$; Fig 2A), and high plasma VEGF-A (categorized at the median as high or low) and worse survival (unadjusted HR, 2.719; 95% CI, 1.160 to 6.374; adjusted HR, 5.298; 95% CI, 2.002 to 14.022; Fig 2C).

Table 2. Patient Characteristics and Activity of Bevacizumab

Characteristics	No. of Patients (N = 52)	%
Age, years		
Median	62	
Range	32-84	
Performance status		
0	34	65.4
1	17	32.7
2	1	1.9
Histology		
Endometrioid	26	50
Serous	14	26.9
Mixed epithelial	5	9.6
Clear cell	4	7.7
Adenocarcinoma, unspecified	1	1.9
Mucinous	1	1.9
Undifferentiated	1	1.9
Tumor grade		
1	3	5.8
2	12	23.1
3	37	71.2
No. of prior regimens		
1	33	63.5
2	19	36.5
Prior radiation therapy	29	55.8
Response		
Complete response	1	1.9
Partial response	6	11.5
Stable disease	26	50.0
Increasing disease	17	32.7
Indeterminate	2	3.8
PFS ≥ 6 months		
No	31	59.6
Yes	21	40.4
No. of treatment cycles		
1	5	9.6
2	15	28.8
3	2	3.8
4	2	3.8
5	3	5.8
6	5	9.6
7	0	0
8+	20	38.5

Abbreviation: PFS, progression-free survival.

Table 3. Adverse Events (N = 52)

Adverse Event	Toxicity Grade* (No. of patients) 0	1	2	3	4	5
Leukopenia	48	4	0	0	0	0
Thrombocytopenia	46	6	0	0	0	0
Neutropenia	50	2	0	0	0	0
Anemia	36	9	6	1	0	0
Hypersensitivity	50	1	1	0	0	0
Rhinitis	50	1	1	0	0	0
Hypertension	43	2	3	4	0	0
Hypotension	50	1	0	1	0	0
Other cardiac	48	3	1	0	0	0
Constitutional	17	23	10	2	0	0
Dermatologic	47	5	0	0	0	0
Nausea	44	6	2	0	0	0
Vomiting	46	4	2	0	0	0
GI	28	21	2	1	0	0
Hemorrhage	40	9	1	1	1	0
Hepatobiliary	51	0	0	1	0	0
Infection	47	0	5	0	0	0
Edema (limb)	48	3	0	1	0	0
Metabolic	30	16	3	1	2	0
Musculoskeletal	48	1	0	3	0	0
Neurosensory	48	4	0	0	0	0
Other neurologic	47	4	0	1	0	0
Ocular/visual	49	3	0	0	0	0
Pain	33	11	4	4	0	0

*The maximum severity of each adverse event per patient, graded according to Common Terminology Criteria for Adverse Events (version 3.0).

DISCUSSION

On the basis of historical controls for inactive cytotoxic and targeted agents investigated in previous GOG phase II trials, bevacizumab is worthy of further investigation based on PFS, with 21 patients (40.4%) surviving progression free for at least 6 months. In addition, seven patients (13.5%) experienced an objective response. This trial, as is the case for most previously completed trials of targeted therapy in recurrent/persistent endometrial cancer, entered all patients without regard to histologic or genomic type.

Endometrial cancers are heterogeneous and can be classified into at least two major types. Type I endometrial cancers, those with endometrioid histology, are the most common and are associated with unopposed estrogen exposure. Type II endometrial cancers have non-endometrioid histology (usually papillary serous or clear cell). Inactivation of the *PTEN* tumor-suppressor gene is the most common genetic defect in endometrial cancers and is seen in up to 83% of endometrioid tumors.[33-36] *PIK3CA* mutation, seen in 36% of endometrial carcinomas, is most frequent in tumors that also have *PTEN* mutation.[37]

GOG endometrial cancer trials are subject to central pathology review and categorization of histologic type. It is of great interest as to whether histologic type can be used as a biomarker of response to targeted therapies as a result of the previously mentioned known

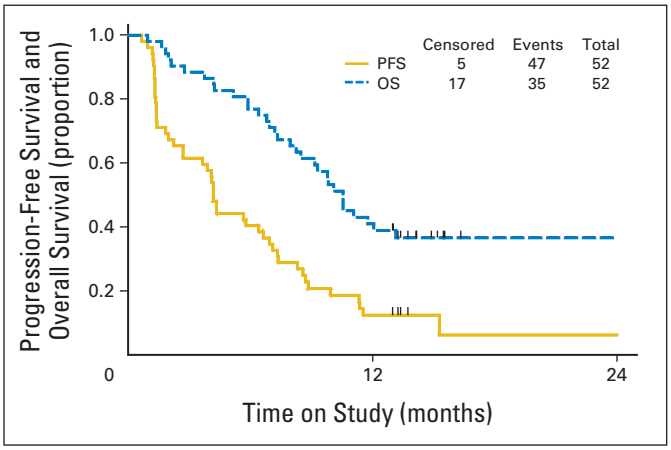

Fig 1. Kaplan-Meier plots demonstrating overall survival (OS) and progression-free survival (PFS) for the 52 patients in the study population.

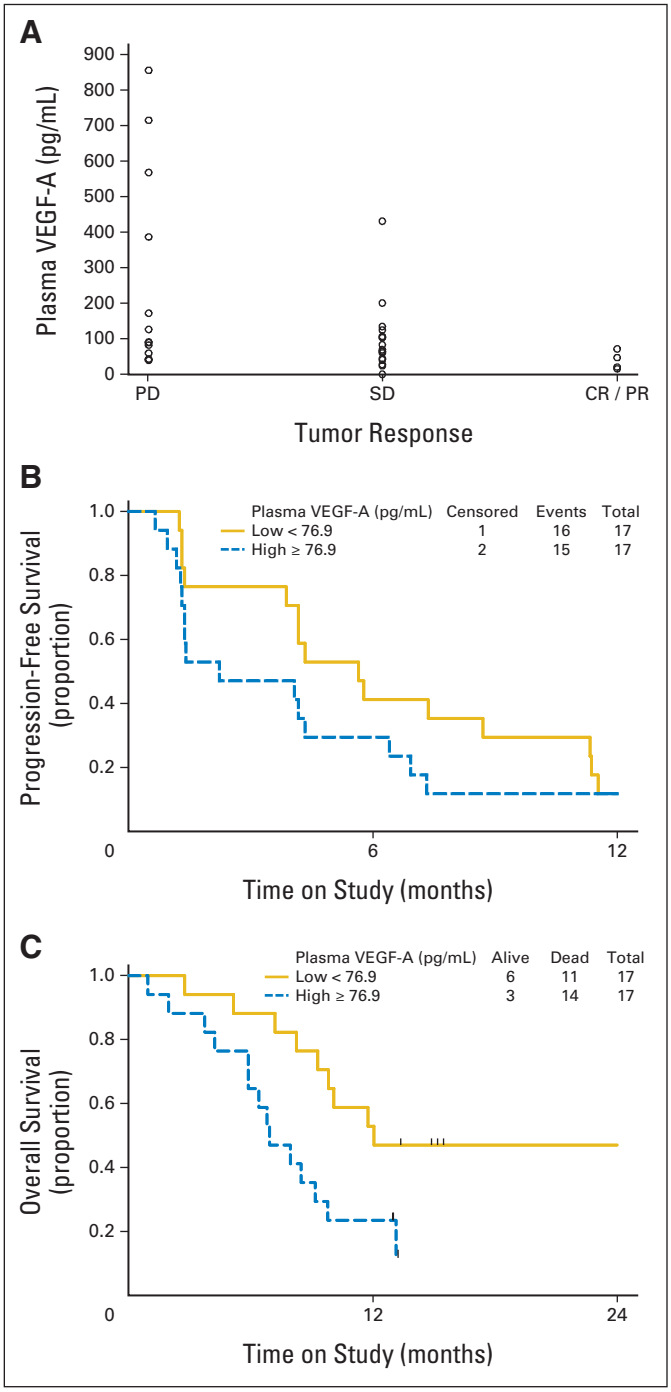

Fig 2. (A) Scatter plot for vascular endothelial growth factor-A (VEGF-A) concentration in pretreatment plasma in picograms per milliliter by clinical tumor response classified as progressive disease (PD), stable disease (SD), and partial response (PR)/complete response (CR). (B) Kaplan-Meier estimates of progression-free survival by pretreatment plasma VEGF-A categorized at the median as low (< 76.9 pg/mL) versus high (≥ 76.9 pg/mL). (C) Kaplan-Meier estimates of overall survival by pretreatment plasma VEGF-A categorized at the median as low (< 76.9 pg/mL) versus high (≥ 76.9 pg/mL).

genetic alterations. In the current study, responses were seen across histologic type (although interestingly, the one patient with a complete response and three of six patients with a partial response had serous histology), and the percentage of patients alive and progression free at 6 months was similar for serous and endometrioid histologies. Patient numbers are too small to formally evaluate the role of histologic subtype and response to bevacizumab in this study, but it is worthy of further study.

Three mammalian target of rapamycin inhibitors, temsirolimus, everolimus, and ridaforolimus, are in clinical trials in endometrial cancer. Preliminary results of a phase II trial of temsirolimus in recurrent or metastatic endometrial cancer (chemotherapy naive) demonstrated encouraging results, with five confirmed partial responses (26%) in 19 evaluable patients.[8] Evaluation of a second cohort, women who must have had treatment with one prior regimen of cytotoxic chemotherapy, revealed an ORR of 7% (two of 27 patients).[9] A phase II trial of everolimus, in patients with one to two prior chemotherapy regimens, reported no responses.[10] Entry was limited to patients with endometrioid histology. A phase II trial of intravenous ridaforolimus in recurrent or metastatic endometrial cancer and carcinosarcoma of the uterus (up to two prior cytotoxic regimens) revealed a response rate of 9% (four of 45 patients).[11]

Epidermal growth factor receptor as a therapeutic target has also been evaluated in endometrial cancer. Erlotinib was evaluated in chemotherapy-naive patients, showing an ORR of 12.5% (four of 32 patients).[13] Gefitinib failed to meet criteria for further evaluation in patients with one to two prior chemotherapy regimens (ORR, 3.8% [one of 26 patients]; 6-month PFS, 8.3% [four of 26 patients]).[14] One (5%) of 20 evaluable patients (one to four prior chemotherapy regimens) treated with cetuximab experienced a partial response.[15] A phase II trial of trastuzumab did select patients based on human epidermal growth factor receptor 2 positivity (either by overexpression or amplification), although it failed to showed responses.[12]

Prior attempts to target VEGF have shown modest activity. Treatment of patients with recurrent/persistent endometrial cancer (one to two prior regimens) with thalidomide yielded an ORR of 12.5% (three of 24 patients), but with only 8.3% of patients (two of 24 patients) surviving progression free for at least 6 months.[16] On preliminary report, the oral tyrosine kinase inhibitors sunitinib and sorafenib have resulted in minimal activity, with ORRs of 15% (three of 20 patients) and 5% (two of 39 patients), respectively.[17]

The most striking translational finding was the relationship of high circulating VEGF-A levels with poor outcome in this study. This raises the following important question: What is the source of circulating VEGF-A? VEGF-A is produced by many cells in the body, including the vascular endothelium, and our finding that archival VEGF-A levels from tissues obtained remote from bevacizumab treatment did not correlate with pretreatment circulating levels suggests that sources other than the tumor contribute to plasma VEGF-A levels. Indeed, although high plasma VEGF-A concentrations assessed by ELISA were associated with lack of tumor response and an increased risk of death, high VEGF-A staining intensity in archival tumor was associated with a reduced risk of death. It is possible that VEGF-A staining in remote archival tumor does not reflect the state of the tumor immediately before treatment when the plasma pretreatment VEGF-A levels were assessed. Pretreatment biopsies of recurrent or persistent lesions were not performed in this study. It is also possible that because of the small patient numbers in this study, this result is spurious. Regardless, these data imply that relying on the tumor phenotype when assessed from archival tissues remote from treatment to predict clinical response may have limitations. Despite the limitations

in sample size and exploratory nature of the studies, angiogenic markers in tumor and serum may provide prognostic value in recurrent/persistent endometrial cancer and are being prospectively evaluated in the GOG randomized phase II trial of paclitaxel, carboplatin, and bevacizumab; paclitaxel, carboplatin, and temsirolimus; and ixabepilone, carboplatin, and bevacizumab.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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